Search result: 1 of 1

(WO/2001/014424) HUMAN CTLA-4 ANTIBODIES AND THEIR USES

Biblio. Data | Description | Claims | National Phase | Notices | Documents

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Abstract: The present invention provides novel human sequence antibodies against human CTLA-4 and methods of treating human diseases, infections and other conditions using these antibodies.

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Note: OCR Text

WHAT IS CLAIMED IS: 1. A human sequence antibody that specifically binds to human CTLA-4.

2. A therapeutically-effective human sequence antibody that specifically binds to human CTLA-4.

3. The therapeutically-effective human sequence antibody of claim 2, wherein the antibody binds CTLA-4 on the cell surface of normal human T cells.

4. The therapeutically-effective human sequence antibody of claim 2, wherein the antibody is well-tolerated in a patient.

5. The therapeutically-effective human sequence antibody of claim 2, wherein the T cell subpopulations marked by CD antigens CD4, CD8, CD25, and CD69 remain stable during and subsequent to the administration of the antibody.

6. An isolated human sequence antibody that specifically binds to human CTLA-4 which is substantially free of non-immunoglobulin associated human proteins.

7. A composition of polyclonal antibodies comprising a plurality of antibodies according to claim 1.

8. The composition of polyclonal antibodies of claim 7 comprising at least about 10 different antibodies according to claim 1.

9. The composition of polyclonal antibodies of claim 7 comprising at least about 100 different antibodies according to claim 1.

10. The composition of polyclonal antibodies of claim 7 comprising at least about 1000 different antibodies according to claim 1.

11. The human sequence antibody of claim, wherein the human antibody blocks binding of human CTLA-4 to B7 ligands.

12. The human sequence antibody of claim 1, wherein the human sequence antibody does not block binding of human CTLA-4 to B7 ligands.

13. The human sequence antibody of claim 1, wherein the antibody binds to human CTLA-4 with an equilibrium association constant (Ka) of at least 108 M-1.

14. The human sequence antibody of claim 1, wherein the antibody binds to human CTLA-4 with an equilibrium association constant (Ka) of at least 109 M-.

15. The human sequence antibody of claim 1, wherein the antibody blocks binding of human CTLA-4 to B7 ligands by at least about 20%.

16. The human sequence antibody of claim 1, wherein the antibody blocks binding of human CTLA-4 to B7 ligands by at least about 30%.

17. The human sequence antibody of claim 1, wherein the antibody blocks binding of human CTLA-4 to B7 ligands by at least about 40%.

18. The human sequence antibody of claim 1, wherein the antibody blocks binding of human CTLA-4 to B7 ligands by at least about 50%.

19. The human sequence antibody of claim 1, wherein the antibody heavy chain is IgG or IgM.

20. The human sequence antibody of claim 19, wherein the IgG antibody heavy chain is IgGI, IgG2, IgG3 or IgG4.

21. The human sequence antibody of claim 1, wherein the antibody light chain is a kappa light chain.

22. The human sequence antibody of claim 1, wherein the human sequence antibody is encoded by human IgG heavy chain and human kappa light chain nucleic acids that comprise nucleotide sequences in their variable regions as set forth in SEQ ID NO: 16 and SEQ ID NO: 6, respectively.

23. The human sequence antibody of claim 1, wherein the human sequence antibody is encoded by human IgG heavy chain and human kappa light chain nucleic acids that comprise nucleotide sequences in their variable regions as set forth in SEQ ID NO: 18 and SEQ ID NO: 8, respectively.

24. The human sequence antibody of claim 1, wherein the human sequence antibody is encoded by human IgG heavy chain and human kappa light chain nucleic acids that comprise nucleotide sequences in their variable regions as set forth in SEQ ID NO: 22 and SEQ ID NO: 12, respectively.

25. A human sequence antibody of claim 1, wherein the human sequence antibody is encoded by heavy chain and light chain variable region amino acid sequences as set for the in SEQ ID NO: 17 and SEQ ID NO: 7, respectively.

26. A human sequence antibody of claim 1, wherein the human sequence antibody is encoded by heavy chain and light chain variable region amino acid sequences as set for the in SEQ ID NO: 19 and SEQ ID NO: 9, respectively.

27. A human sequence antibody of claim 1, wherein the human sequence antibody is encoded by heavy chain and light chain variable region amino acid sequences as set for the in SEQ ID NO: 23 and SEQ ID NO: 13, respectively.

28. The human sequence antibody of claim 1, wherein the human sequence antibody is encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising variable heavy and light chain sequences from V gene segments VH 3-30.3 and VK A-27, respectively.

29. The human sequence antibody of claim 1, wherein the human sequence antibody is encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising variable heavy and light chain sequences from V gene segments VH 3-33 and VK L-15, respectively.

30. The human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO: 27), FISYDGNNKYYADSVKG (SEQ ID NO: 32) and TGWLGPFDY (SEQ ID NO: 37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVGSSYLA (SEQ ID NO: 24), GAFSRAT (SEQ ID NO: 29), and QQYGSSPWT (SEQ ID NO: 35), respectively.

31. The human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO: 27), FISYDGSNKHYADSVKG (SEQ ID NO: 33) and TGWLGPFDY (SEQ ID NO: 38), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVSSSFLA (SEQ ID NO: 25), GASSRAT (SEQ ID NO: 30), and QQYGSSPWT (SEQ ID NO: 35), respectively.

32. The human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYGMH (SEQ ID NO: 28), VIWYDGSNKYYADSVKG (SEQ ID NO: 34) and APNYIGAFDV (SEQ ID NO: 39), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQGISSWLA (SEQ ID NO: 26), AASSLQS (SEQ ID NO: 31), and QQYNSYPPT (SEQ ID NO: 36), respectively.

33. The human sequence antibody of claim 1, wherein said human sequence antibody is produced by a transgenic non-human animal.

34. The human sequence antibody of claim 33, wherein said transgenic non-human animal is a mouse.

34. The human sequence antibody of claim 33, wherein said transgenic non-human animal is a mouse.

35. The human sequence antibody of claim 1, wherein the human sequence antibody is a Fab fragment.

36. A polyvalent complex comprising at least two human sequence antibodies each of which specifically binds to human CTLA-4.

37. The polyvalent complex of claim 36, wherein the two different antibodies are linked to each other covalently.

38. The polyvalent complex of claim 36, wherein the two different antibodies are linked to each other non-covalently.

39. A nucleic acid encoding a heavy chain of a human sequence antibody.

40. The nucleic acid of claim comprising the nucleotide sequence as set forth in SEQ ID NO: 1.

41. A transgenic non-human animal having a genome comprising a human sequence heavy chain transgene and a human sequence light chain transgene, which animal has been immunized with a human CTLA-4, or a fragment or an analog thereof, whereby the animal expresses human sequence antibodies to the human CTLA-4.

42. The transgenic non-human animal of claim 41, wherein the transgenic non-human animal is a transgenic mouse.

43. The transgenic mouse of claim 42 comprising HCo7 or HCo 12.

44. A cell line comprising a B cell obtained from a transgenic non-human animal having a genome comprising a human sequence heavy chain transgene and a human sequence light chain transgene, wherein the hybridoma produces a human sequence antibody that specifically binds to human CTLA-4.

45. The cell line of claim 44, wherein the cell line is a hybridoma.

46. A hybridoma secreting a human sequence antibody that specifically binds human CTLA-4 or binding fragment thereof, wherein the antibody is selected from the group consisting of : a human sequence antibody comprising heavy chain heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO: 27), FISYDGNNKYYADSVKG (SEQ ID NO: 32) and TGWLGPFDY (SEQ ID NO: 37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVGSSYLA (SEQ ID NO: 24), GAFSRAT (SEQ ID NO: 29), and QQYGSSPWT (SEQ ID NO: 35), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO: 17 and SEQ ID NO: 7, respectively, a human sequence antibody comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO: 27), FISYDGSNKHYADSVKG (SEQ ID NO: 33) and TGWLGPFDY (SEQ ID NO: 38), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVSSSFLA (SEQ ID NO: 25), GASSRAT (SEQ ID NO: 30), and QQYGSSPWT (SEQ ID NO: 35), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO: 19 and SEQ ID NO: 9, respectively, and a human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYGMH (SEQ ID NO: 28), VIWYDGSNKYYADSVKG (SEQ ID NO: 34) and APNYIGAFDV (SEQ ID NO: 39), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQGISSWLA (SEQ ID NO: 26), AASSLQS (SEQ ID NO: 31), and QQYNSYPPT (SEQ ID NO: 36), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO: 23 and SEQ ID NO: 13, respectively.

47. A pharmaceutical composition comprising a human sequence antibody of claim and a pharmaceutically acceptable carrier.

48. The pharmaceutical composition of claim 47, further comprising an agent effective to induce an immune response against a target antigen.

49. The pharmaceutical composition of claim 47, further comprising a chemotherapeutic agent.

50. The pharmaceutical composition of claim 47, further comprising an antibody to an immunosuppressive molecule.

51. A method for inducing, augmenting or prolonging an immune response to an antigen in a patient, comprising administering a therapeutically effective amount of a pharmaceutical composition of claim 47, wherein the pharmaceutical composition blocks binding of human CTLA-4 to human B7 ligands.

52. The method of claim 51, wherein the antigen is a tumor antigen or an antigen from a pathogen.

53. The method of claim 52, wherein the patient is also treated with a bispecific antibody, said bispecific antibody comprising an antibody sequence having an affinity for an antigen from a tumor or a pathogen.

54. The method of claim 52, wherein the pathogen is a virus, a bacterium, a fungus or a parasite.

55. The method of claim 54, wherein the pathogen is HIV.

56. The method of claim 51, further comprising administering the antigen, or a fragment or an analog thereof, to the patient, whereby the antigen in combination with the human sequence antibody induces, augments or prolongs the immune response.

57. The method of claim 56, wherein the antigen is a tumor antigen or an antigen from a pathogen.

58. The method of claim 57, wherein the tumor antigen is telomerase.

59. The method of claim 56, wherein the antigen is a component of an amyloid formation in the patient.

60. The method of claim 56, wherein the patient is suffering from Alzheimer's disease and the antigen is AB peptide.

61. The method of claim 51, further comprising administering a cytokine to the patient.

62. A method of suppressing an immune response in a patient, comprising administering to the patient a therapeutically effective dosage of a polyvalent preparation comprising at least two human sequence antibodies to human CTLA-4 linked to each other.

63. A method of suppressing an immune response in a patient, comprising administering to the patient a therapeutically effective dosage of a polyclonal preparation comprising at least two human sequence antibodies to human CTLA-4.

64. A method of treating an autoimmune disease in a subject caused or exacerbated by increased activity of T cells consisting of administering a theraputically effective amount of a pharmaceutical composition of claim 47 to the subject.

65. A method of treating cancer in a subject consisting of administering a therapeutically effective amount of a pharmaceutical composition of claim 47 to the subject.

66. The method of claim 65, wherein the cancer is prostate cancer, melanoma, or epithelial cancer.

67. The method of claim 65, further comprising a vaccine.

68. The method of claim 67, wherein the vaccine is a tumor cell vaccine, a GM-CSF-modified tumor cell vaccine, or an antigen-loaded dendritic cell vaccine.